REMARKS

Claims 20-33 are pending and under examination in the subject application. Applicants have hereinabove amended claims 20 and 30. Applicants note that these are merely minor formatting changes. Applicants maintain that these amendments raise no issue of new matter, and respectfully request entry of this Amendment. Upon entry of this Amendment, claims 20-33 will be pending and under examination.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the January 27, 2005 Office Action have been overcome and respectfully request that the Examiner reconsider and withdraw same.

Rejection Under 35 U.S.C. §102(a)

The Examiner rejected claims 20 and 21 under 35 U.S.C. §102(a) for allegedly being anticipated by Myrick et al. (*FASEB Journal* (1997) 11: abstract A546) (hereinafter "Myrick et al. (I)"). The Examiner stated that Myrick et al. (I) was provided by applicants on PTO-1449, dated June 18, 2004, and is available as prior art with a date of 1997.

The Examiner stated that Myrick et al. (I) teaches that treatment of Jurkat T-cells, a leukemic cell line, with paclitaxel and ceramide results in 87% growth inhibition through cell cycle arrest and apoptosis. The Examiner stated that Myrick et al. (I) also teaches the addition of paclitaxel followed by ceramide as well as the reverse.

The Examiner stated that Myrick et al. (*FASEB Journal* (1999) 13: page A191, abstract 177.2) (hereinafter "Myrick et al.

(II)") is viewed as an equivalent teaching to Myrick et al. (I).

In response, applicants respectfully traverse the Examiner's rejection, and maintain that Myrick et al. (I) and Myrick et al. (II) are not prior art against the rejected claims. In support of their position, applicants submit a Declaration Under 37 C.F.R. §1.132 (Exhibit 1). In this Declaration, inventor Dr. Harold Wanebo declares that (a) he and co-inventor Dr. Shashikant Mehta conceived of the subject invention and are co-authors of Myrick et al. (I) and Myrick et al. (II), and (b) the other co-authors of Myrick et al. (I) and Myrick et al. (II) did not contribute to the conception of the invention as claimed. Therefore, Myrick et al. (I) and Myrick et al. (II) are not prior art under 35 U.S.C. §102(a), since the invention was not "known or used *by others*...before the invention thereof by the applicant for patent." 35 U.S.C. §102(a).

In view of the above remarks, applicants maintain that claims 20 and 21 satisfy the requirements of 35 U.S.C. §102(a).

Rejection Under 35 U.S.C. §102(e)

The Examiner rejected claims 20, 22-25 and 27-31 under 35 U.S.C. §102(e) as allegedly anticipated by Joshi et al. (U.S. Patent 6,841,537 B1) which claims benefit of provisional application 60/111,637, filed on December 9, 1998.

The Examiner stated the following regarding Joshi et al. Joshi et al. teaches a method of cancer therapy where the cancer cells are transformed with nucleic acids that encode gene

products to inhibit growth of the cancer cells (abstract). The method includes administering to a cancer patient a nucleic acid (also referred to as a foreign therapeutic gene) that transforms the cancer cells and inhibits their growth by inducing apoptosis; and further administering paclitaxel as a cell cycle synchronizer to enhance the effect of the foreign therapeutic gene ('537 claims 1, 8, 9, 15, 16, 22 and 23). The paclitaxel is in a liposomal formulation of instant claims 23 and 29, of which ceramide is listed as an example (citing the specification at column 7, line 64; and claims 9 and 23). The administration techniques of instant claims 24 and 29 at column 16, lines 60 et seq. of the specification, include intravenous injection. Joshi et al. teach the treatment of human colon adenocarcinoma, human ovarian carcinoma, mouse melanoma, lung carcinoma, of the Markush groups of claims 20, 25, 30 and 31 (citing specification page 16, lines 21-28).

In response, applicants respectfully traverse the Examiner's rejection.

Briefly, claims 20, 22-25 and 27-31 provide a method for inducing apoptosis in a cell by contacting the cell with the specific combination of *C_6-ceramide and paclitaxel*.

Joshi et al. do not teach or suggest the use of C_6-ceramide for inducing apoptosis in a cell, and indeed, do not recite any use of C_6-ceramide, as opposed to ceramide generally. Joshi et al. therefore do <u>not</u> teach a method for inducing apoptosis in a cell comprising contacting the cell with a combination of paclitaxel and C_6-ceramide and thus, fail to teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that the pending claims satisfy the requirements of 35 U.S.C. §102(e).

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 20, 25, 26, 30 and 31-33 under 35 U.S.C. §103(a) as allegedly unpatentable over Jayadev et al. in view of Mycek et al., and U.S. Patent Nos. 5,597,830 and 6,147,060.

The Examiner stated that Jayadev et al. teach that ceramide causes significant arrest in the G_0/G_1 phase, with pronounced apoptosis, in Molt-4 leukemia cells (abstract). The Examiner stated that Jayadev et al. do not teach treatment with paclitaxel.

The Examiner stated that Mycek et al. teach that paclitaxel blocks mitosis in the G_2-M phase by reversibly binding to tubulin, stabilizing the microtubules, causing the cells to remain in metaphase, and thereby causing cell death. The Examiner stated that Mycek et al. do not teach treatment with ceramide.

The Examiner asserted that it is known in the field of cancer chemotherapy that combination chemotherapy is more effective than single-drug treatment in most cancers for which chemotherapy is effective. The Examiner stated that cytotoxic agents with different molecular sites and mechanisms of action are usually combined at full doses, resulting in better response rates (citing Mycek et al. at page 376). The Examiner stated that in addition, U.S. Patent Nos. 5,597,830 and 6,147,060 teach combination chemotherapy for cancer using

multiple drugs.

The Examiner stated that the teaching of combinatorial chemotherapy ('830 and '060 patents) in cancer treatment would have motivated one of ordinary skill in the art to have used the two drugs for their known modes of action in the cell cycle to effect the desired treatment of the cancer at multiple levels. The Examiner stated that it would have been obvious to one of ordinary skill in the art of cancer treatment to combine paclitaxel and ceramide (both known to treat cancer) since they work at different times during the cell cycle.

In response to the Examiner's rejection, applicants respectfully traverse and maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Claims 20 and 25 provide methods which comprise increasing apoptosis in a cell or decreasing the size of a tumor by contacting the cell or tumor with C_6-ceramide and paclitaxel, respectively. Claim 30 provides a pharmaceutical composition comprising C_6-ceramide and paclitaxel which causes apoptosis of a cancer cell.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed

invention would succeed.

Applicants contend that the references cited against the rejected claims fail to support a *prima facie* case of obviousness, in that they fail to create a reasonable expectation of success.

Without experimentation, one of ordinary skill cannot reasonably predict that a successful anti-cancer outcome, not to mention a synergistic outcome, will occur using a *particular combination of two drugs*, even though each drug, when used individually, has anti-cancer effects. For example, in Mycek et al., the authors state that combination therapy using paclitaxel with other anticancer drugs is being *evaluated* (see page 392). In other words, each specific combination of two or more anti-cancer agents must be tested before one of skill in the art can know that such combination will be effective against cancer, let alone more effective than either agent alone. The Examiner has failed to show otherwise.

Underscoring the unpredictability of success when combining two anti-cancer agents is U.S. Patent No. 5,597,830, wherein the inventors demonstrate that there are limitations to combination therapy and that anti-cancer agents such as taxol and other taxanes are actually *inhibited* by the oncolytic agent Suramin (see col. 4; Figure 3; and Figure 6).

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 20, 25, 26, 30 and 31-33 over these references.

In view of the above remarks, applicants maintain that claims 20, 25, 26, 30 and 31-33 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

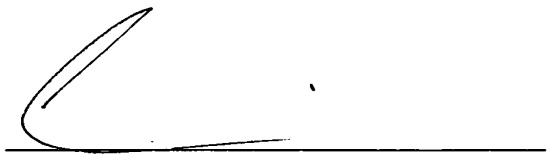
Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed $510.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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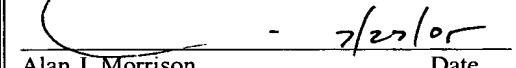
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



7/20/05

Alan J. Morrison — Date
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